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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,300	09/18/2006	Matthias Ebert	MST-2390.1	3699

7590 01/29/2008

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
01/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/575,300	Applicant(s) EBERT ET AL.	
	Examiner Sean E. Aeder	Art Unit 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 19 December 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 2 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): the rejection of claim 1 under 35 U.S.C. 112 second paragraph.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-11,14,16 and 18-24*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Misook Yu/
Primary Examiner, 1642

Continuation of 11. does NOT place the application in condition for allowance because:

Claims 1-11,14,16 and 18-24 remain rejected under 35 U.S.C. 112 first paragraph for failing to comply with both the written description requirement and the enablement requirement.

In regards to the written description rejection, Applicant repeats previously presented arguments. Applicant further states that the prior art of Ivanov et al (Am. J. Path., 2001, 158(3):905-919) teaches the genus of diseases subject to the claimed methods. Applicant further states the number of diseases within the genus is fairly limited, as shown by exemplary diseases recited in claim 3 and disclosed in the instant specification. Applicant further states that one of skill in the art would reasonably expect normal tissues with high expression of CA IX (in addition to gastric mucosa, gallbladder, and bilary epithium), primarily normal tissue with high rates of proliferation, would be expected to lose CA IX expression upon carcinogenesis. Applicant further states that case law supports the view that some inoperative embodiments are permissible and that the subject matter within a claim need not be shown to have the same degree of utility. Applicant further cites the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112 first paragraph: "descriptions of a representative number of species does not require that the description be of such specificity that it would provide individual support for each species that the genus embraces". Applicant further cites Robertson et al and states that Roberton et al support a prediction that high CA IX expression in a tumor would be associated with a poorer prognosis in a broad range of precancerous and cancerous diseases. Applicant again submits that the Lilly case is not relevant to the instant claims. Applicant states that the "genetic material" found to lack written description in Eli Lilly was the human insulin gene for which the native DNA sequence was not provided. Applicant states that in the instant case, the claimed methods use the product MN/CA IX protein or MN/CA IX polypeptide, which are adequately described in the specification. Applicant further states that the products being used according to the claims is not the disease and the specific diseases comprised within the genus are basically finite and not unknown. Applicant further states that the genus of samples and how to handle the samples are well known in the art.

The amendments to the claims and the arguments found in the After Final of 12/19/07 have been carefully considered, but are not deemed persuasive. In regards to previously presented arguments, previously presented arguments have been addressed in previous Office Actions. In regards to the statement that the prior art of Ivanov et al (Am. J. Path., 2001, 158(3):905-919) teaches the genus of diseases subject to the claimed methods, Ivanov et al provides a limited number of species encompassed by the genus. However, the specification and the art have not provided a sufficient disclosure as to which cancers would and would not be accompanied by a decrease in MN/CA IX upon carcinogenesis. In regards to the argument that the number of diseases within the genus is fairly limited, as shown by exemplary diseases recited in claim 3 and disclosed in the instant specification, Applicant's arguments are not in commensurate with the scope of the claims. The claims are not limited to those recited in claim 3 or disclosed in the instant specification. The examiner disagrees with the argument that one of skill in the art would reasonably expect normal tissues with high expression of CA IX (in addition to gastric mucosa, gallbladder, and bilary epithium), primarily normal tissue with high rates of proliferation, would be expected to lose CA IX expression upon carcinogenesis. Such a trend is not demonstrated by the prior art or the specification. In regards to the argument that case law supports the view that some inoperative embodiments are permissible and that the subject matter within a claim need not be shown to have the same degree of utility, the instant rejection is based on whether the invention is adequately described and is not based on the operability or utility of the claims. In regards to the citation of the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112 first paragraph "descriptions of a representative number of species does not require that the description be of such specificity that it would provide individual support for each species that the genus embraces", the species disclosed in the specification and found in the prior art are not a "representative number" of species. The species disclosed in the specification and found in the prior art do not demonstrate which other tissue samples are from a disease that affects a tissue which normally expresses MN/CA IX protein but loses or has significantly reduced MN/CA IX expression upon carcinogenesis. In regards to the citation of Robertson et al and statement that Robertson et al supports a prediction that high CA IX expression in a tumor would be associated with a poorer prognosis in a broad range of precancerous and cancerous diseases, said statement is related to enablement and the test for adequate written description is separate and distinct from the test under enablement criteria of 35 U.S.C. 112 first paragraph. In regards to the argument that the Lilly case is not relevant to the instant claims and that MN/CA IX protein or MN/CA IX polypeptide are adequately described in the specification (unlike the "genetic material" found to lack written description in Eli Lilly for which the native DNA sequence was not provided), the genus lacking a written description in the instant case is not MN/CA IX protein or MN/CA IX polypeptide. Rather, the genus lacking written description in the instant case is a genus of tissue samples from a disease that affects a tissue which normally expresses MN/CA IX protein but loses or has significantly reduced MN/CA IX expression upon carcinogenesis. Just as Lilly et al lacked a written description for a native DNA sequence that was not provided, the instant case lacks a written description for a genus of tissue samples from a disease that affects a tissue which normally expresses MN/CA IX protein but loses or has significantly reduced MN/CA IX expression upon carcinogenesis. In regards to the argument that the product being used according to the claims is not the disease and the specific diseases comprised within the genus are basically finite and not unknown, the products being used according to the claims are tissue samples from a disease that affects a tissue which normally expresses MN/CA IX protein but loses or has significantly reduced MN/CA IX expression upon carcinogenesis. Other than a few species, other members of the genus remain unknown. The disclosed or taught species do not provide an indication of what else would be included in the genus. In regards to the argument that the genus of samples and how to handle the samples are well known in the art, the genus of tissue samples from a disease that affects a tissue which normally expresses MN/CA IX protein but loses or has significantly reduced MN/CA IX expression upon carcinogenesis is not well known.

In regards to the enablement rejection, Applicant repeats previously presented arguments. Applicant further questions what Examiner meant by "every type of prognosis". Applicant further states that no evidence has been presented as to why the methods would not work as claimed. Applicant further states that once a pattern of prognosis for a genus of diseases is established, it is conventional to apply those patterns for those diseases in the absence of evidence to the contrary. Applicant further sates that the standard for enablement is not absolute certainty but whether "it is more likely than not true" (MPEP 2164.07) and case law supports the view that some

inoperative embodiments are permissible. Applicant again argues that recent data reported in Robertson et al 2004 (indicating MN/CA IX's role in tumorigenesis) support the instant claims. Applicant further states that the Examiner has not provided any examples where the claimed prognostic methods do not work for any type of prognosis of preneoplastic/neoplastic diseases of tissues where MN/CA IX is normally expressed but expression is lost or diminished upon carcinogenesis. Applicant further states that, in view of the disclosure, all that is left to one of skill in the art to perform the claimed methods would be routine experimentation. Applicant further states that the number of preneoplastic/neoplastic diseases to which the claimed methods apply is relatively small. Applicant further states that there is no suggestion in Tockman et al that one of skill in the art would not know how to correlate a tumor marker with a particular prognosis. Applicant further argues that Tockman et al does not constitute evidence to the contrary and states that Tockman et al does not describe any subject preneoplastic/neoplastic disease of a tissue in which normal MN/CA IX expression is lost upon carcinogenesis and which renewed MN/CA IX expression is associated with a better prognosis. Applicant further cites Pastrokevo and Zavada and states that the link between high MN/CA IX expression and poor prognosis has been established in general for tissues in which MN/CA IX is normally not expressed. Applicant further states that MN/CA IX behaves predictably in those tissue with one apparent exception being renal cell carcinoma, and suggests reasons why lower MN/CA IX expression in renal cell carcinoma is indicative of a poor prognosis. Applicant further questions whether Examiner is suggesting that it is necessary for Applicant to identify the mechanism by which higher MN/CA IX leads to poor prognosis. Applicant further argues that Robertson et al and others predict that MN/CA IX levels should correlate with survival, disease recurrence, and response to treatment in subjects, as MN/CA IX has an important functional role in tumorigenesis and one of skill in the art would expect that high MN/CA IX would correlate with several endpoints of prognosis. Applicant further indicates that the instant method would not require undue experimentation and states that the Board in Ex parte Mark, 12 USPQ 1904 (PTO Bd. App. & Interf. 1989) reversed an examiner's undue experimentation rejection based on the "limited successful embodiments shown and the established unpredictability associated with...site-specific mutagenesis...to obtain even one biologically active mutein".

The amendments to the claims and the arguments found in the After Final of 12/19/07 have been carefully considered, but are not deemed persuasive. In regards to previously presented arguments, previously presented arguments have been addressed in previous Office Actions. In regards to what Examiner meant by "every type of prognosis", Applicant is directed to page 9 of the specification. Page 9 of the specification discloses that types of prognosis include (1) survival, (2) risk of recurrence, and (3) response to treatment (see lines 22-25 on page 9). Each of said type of prognosis represent a particular type of disease state. In regards to the argument that no evidence has been presented as to why the methods would not work as claimed, (1) Tockman et al provides evidence that the state of the art for using expression of a particular marker as an indication of a particular diseased state is unpredictable and (2) Pastrokevo and Zavada provide evidence demonstrating that decreased expression of MN/CA IX correlates with poorer survival in renal cell carcinoma patients, while the instant claims are drawn to methods wherein overexpression of MN/CA IX in samples from a genus of patients correlates with a poor prognosis. In regards to the argument that once a pattern of prognosis for a genus of diseases is established, it is conventional to apply that pattern for those diseases in the absence of evidence to the contrary, Tockman et al and Pastrokevo and Zavada provide evidence why one would not predict a single pattern of prognosis for the genus of diseases encompassed by the claimed methods. In regards to the argument that the standard for enablement is not absolute certainty but whether "it is more likely than not true" (MPEP 2164.07) and case law supports the view that some inoperative embodiments are permissible, Applicant is again directed to the teachings of Tockman et al and Pastrokevo and Zavada discussed above and in the Office Action of 10/19/07. In regards to the argument that recent data reported in Robertson et al 2004 (indicating MN/CA IX's role in tumorigenesis) support the instant claims, the data reported in Robertson et al does not demonstrate the claimed method wherein elevated expression of MN/CA IX protein results in decreased survival, higher risk of recurrence, and poorer response to treatment. In regards to the argument that the Examiner has not provided any examples where the claimed prognostic methods do not work for any type of prognosis of preneoplastic/neoplastic diseases of tissues where MN/CA IX is normally expressed but expression is lost or diminished upon carcinogenesis, the Examiner has provided evidence demonstrating that undue experimentation would be required to practice the method in commensurate with the scope of the claims based on the factors summarized in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (see pages 12-14 of the Office Action of 10/19/07). In regards to the argument that all that is left to one of skill in the art to perform the claimed methods would be routine experimentation, undue experimentation would be required to practice the method in commensurate with the scope of the claims based on the factors summarized in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (see pages 12-14 of the Office Action of 10/19/07). In regards to the argument that the number of preneoplastic/neoplastic diseases to which the claimed methods apply is relatively small, it is unclear which preneoplastic/neoplastic diseases are encompassed by the claimed methods (see written description rejection above) and it would require undue experimentation to identify said diseases. In regards to the argument that there is no suggestion in Tockman et al that one of skill in the art would not know how to correlate a tumor marker with a particular prognosis, Tockman et al teaches that prior to successful application of newly described markers, research must validate said markers against known disease end points (see abstract, in particular). In regards to the argument that Tockman et al does not constitute evidence to the contrary and that Tockman et al does not describe any subject preneoplastic/neoplastic disease of a tissue in which normal MN/CA IX expression is lost upon carcinogenesis and which renewed MN/CA IX expression is associated with a better prognosis, Tockman is cited to demonstrate the state of the art and the unpredictability of the art. In regards to the citation of Pastrokevo and Zavada and statement that the link between high MN/CA IX expression and poor prognosis has been established in general for tissues in which MN/CA IX is normally not expressed, Pastrokevo and Zavada provide evidence demonstrating that decreased expression of MN/CA IX correlates with poorer survival in renal cell carcinoma patients, while the instant claims are drawn to methods wherein overexpression of MN/CA IX in samples from a genus of patients correlates with a poor prognosis. In regards to the argument that MN/CA IX behaves predictably in those tissue with one apparent exception being renal cell carcinoma, and suggests reasons why lower MN/CA IX expression in renal cell carcinoma is indicative of a poor prognosis, a demonstration that lower MN/CA IX expression is indicative of a poor prognosis in one disease and that elevated MN/CA IX is indicative of a poor prognosis in another disease highlights the unpredictability of using a particular expression level of a particular marker for determining a particular prognosis for patients with a particular diseases unless said particular expression level of said particular marker has been shown to correlate with said particular prognosis for said particular disease. In regards to the question whether Examiner is suggesting that it is necessary for Applicant to identify the mechanism by which higher MN/CA IX leads to poor prognosis, the Examiner is not making said suggestion. In regards to the argument that Robertson et al and others predict that MN/CA IX levels should correlate with survival, disease recurrence, and response to treatment in subjects, as MN/CA IX has an important functional role in tumorigenesis and one of skill in the art would expect that high MN/CA IX would correlate with several endpoints of prognosis, Applicant is directed to the teachings of Tockman et al and Pastrokevo and Zavada discussed above and

in the Office Action of 10/19/07. In regards to the argument that the instant claims would not require undue experimentation and states that the Board in Ex parte Mark, 12 USPQ 1904 (PTO Bd. App. & Interf. 1989) reversed an examiner's undue experimentation rejection based on the "limited successful embodiments shown and the established unpredictability associated with...site-specific mutagenesis...to obtain even one biologically active mutein", Applicant is reminded that each case is examined on its own merits and the reasons why the instant claims would require undue experimentation are discussed above and in the Office Action of 10/19/07.